Chapter 1

Introduction

1.0 Impact of ETS on the Health of Californians

Disease risks due to inhalation of tobacco smoke are not limited to smokers, but extend to nonsmokers who inhale environmental tobacco smoke (ETS) at home, or work, or in public places. Authoritative reviews over the past two decades have presented scientific evidence linking ETS exposures to a number of adverse health outcomes. *Smoking and Health: A Report of the Surgeon General* (U.S. DHEW, 1979) noted several adverse respiratory outcomes in children and adults, as well as some acute cardiovascular effects associated with involuntary exposure to tobacco smoke. The 1982 *A Report of the Surgeon General* (U.S. DHHS, 1982), which focused on the carcinogenic effects of active smoking, raised the concern that involuntary smoking may cause lung cancer. The large series of epidemiological investigations following the publication of that report provided compelling evidence of a causal relationship and subsequently the 1986 *Report of the Surgeon General* (U.S. DHHS, 1986), as well as reviews by the National Research Council (NRC, 1986) and the U.S. Environmental Protection Agency (U.S. EPA, 1992), concluded that ETS exposure causes lung cancer. The NRC (1986) and U.S. EPA (1992) also found ETS exposure to be associated with lower respiratory tract illnesses in young children, as well as with other adverse respiratory outcomes.

Many people are exposed to ETS. Table 1.1 presents estimates of impacts for some of the health effects associated with ETS exposure, and predictions of the numbers of people potentially affected in California, mainly based on extrapolations from national estimates. Recent State and local restrictions on smoking at work and in public places in California, in addition to the California Department of Health Services' (CDHS) advertisement campaign by the Tobacco Control Program, have significantly reduced ETS exposures of nonsmokers in California. Thus the predictions in Table 1.1 may overstate the number of Californians adversely impacted by ETS. Results of the California Adult Tobacco Survey (CDHS, 1995) suggest, however, that it is doubtful that the risks are overstated by more than two-fold. Exposure to ETS therefore remains a significant public health concern in California.

Evidence on ETS-related effects has expanded considerably since the major comprehensive reviews contained in the *Reports of the Surgeon General* and published by U.S. EPA and NRC. The State of California has therefore undertaken a broad review of ETS, covering the major health endpoints potentially associated with ETS exposure.

1.1 Organization of the report

The review begins with introductory material on definitions and the methodology of the review. In Chapter 2 an overview is presented on measurements of ETS exposure, particularly as they relate to characterizations of exposure in epidemiological investigations, and on prevalence of ETS exposure found in studies conducted in

California and nationally. Chapters 3 through 5 address the developmental and reproductive effects of ETS exposure. Perinatal manifestations of developmental toxicity are addressed in Chapter 3, postnatal manifestations in Chapter 4, and male and female reproductive effects in Chapter 5. In Chapter 6, acute and chronic respiratory health effects are described, including some that, under standard definitions (see *e.g.*, U.S. EPA, 1991; CDHS, 1991), are considered to be developmental effects, such as pulmonary development and childhood asthma induction. Chapter 7 describes the evidence for carcinogenic effects of ETS exposure; beginning with a discussion of all sites combined for children and adults, the chapter then describes the evidence for specific sites: lung, nasal sinus, cervical and bladder cancer (sites for which active smoking has been causally linked to cancer induction), and breast, stomach, brain, leukemia, lymphomas, non-Hodgkin's lymphomas and other rare childhood cancers (sites for which there is equivocal evidence for an etiologic role for active smoking). Chapter 8 reviews the evidence for the impact of ETS exposure on coronary heart disease.

1.2 Definition of ETS

ETS is also called "second-hand smoke", and ETS exposure is frequently used interchangeably with "involuntary smoking" and "passive smoking." ETS is formed from the smoldering of a cigarette or other tobacco product, and from smoke exhaled by the smoker (NRC, 1986). There are other minor contributors such as the smoke that escapes while the smoker inhales, and some vapor-phase components that diffuse into the environment. Once released into the environment of the smoker, components are diluted by the ambient air, diffusing in and being transported through it. These smoke constituents may also aggregate with other components in the air, and further age and change in character. This complex mixture is defined as ETS, and inhalation of it, as ETS exposure. In some ways this may be an overly restrictive definition when it comes to assessing effects from prenatal smoke exposures. Because the fetus cannot actively smoke, all of its exposure to tobacco smoke constituents is "passive" or "involuntary". Nonetheless, exposure of the fetus due to maternal smoking during pregnancy is not considered to be ETS exposure in this report.

1.3 Methodology

This review is based on exhaustive searches of the literature, including electronic searches (*e.g.*, Medline, Toxline), formal requests for information through an initial "data call-in" through mailed notices and a *California Regulatory Notice Register* announcement, and less formal requests at a number of public workshops as well as through the public review process. While published, peer-reviewed literature serves as the primary source of data, additional sources, for example from abstracts of meeting presentations or doctoral dissertations, may be included, particularly if they provide information in an area where data are lacking.

Methodological issues that were considered in the review of the epidemiologic literature include: 1) the sample size of the study, which affects the power to detect an effect; 2) the extent to which the analysis or design takes into account potential confounders, or other risk factors; 3) selection bias, or whether the study groups were comparable; and 4)

the potential for bias in ascertaining exposure. These factors were considered when identifying those studies of highest quality.

An important consideration in exploring the effects of ETS exposure is the biological plausibility of an effect. This issue is addressed by comparing findings from studies of ETS exposure to those of active smoking, and by examining the results of animal studies, short term tests and biomarker investigations.

1.3.1 Measures of Exposure in Epidemiological Studies

Characterization of ETS exposure in most epidemiological studies is limited to broad categories (*e.g.*, yes/no, number of hours per week). Accurate categorization is difficult, given the large variation in exposures individuals experience. Exposure has generally been determined in three ways: ascertainment of spousal smoking status; estimation of the number of hours a person is exposed (at home, at work, or elsewhere); or measurement of biomarkers. Interviews or questionnaires are often used to collect the first two types of information. Some of the limitations of assessing ETS exposure are briefly discussed below, while Chapter 2 provides more detail on exposure measurement using biomarkers, and examines issues regarding the use of questionnaires.

Misclassification is an important consideration when reviewing epidemiologic studies. Misclassification of exposure status occurs when individuals are categorized as being more or less exposed than they actually were. If the likelihood of misclassification does not depend on whether the study subjects are diseased or not (that is, misclassification is "nondifferential"), then an association between ETS and the disease will be more difficult to detect. Misclassification is a concern in studies which rely on the ascertainment of spousal smoking status, because ETS exposures also occur outside the home. In addition, the amount smoked by the spouse outside and inside the home, as well as the time spent in the home by the nonsmoking spouse, varies from couple to couple. Other considerations include size and ventilation of the subjects' residences. Misclassification can occur when exposures observed at one point in time are assumed to apply to other time periods. Misclassification can also be an issue when exposure is determined by asking subjects about the number of hours they are exposed, for example, at home or work. While questions on number of hours exposed provide more information about multiple exposure sources, respondents may vary in their awareness of and ability to quantify their exposure (Coultas *et al*., 1989). The tendency is toward underestimation of hours exposed (Emmons *et al*., 1992). Few studies of this type attempt to verify self-reported exposures.

To minimize misclassification errors, the occurrence and duration of exposure to all sources of ETS should be ascertained as completely as possible. More recent studies have used measurement of biomarkers of exposure to improve assessment of ETS exposure. The biomarker cotinine, a metabolite of nicotine with relatively short half-life (20-30 hours in blood plasma), is useful in categorizing and verifying recent exposure. However, because it only reflects exposures of the past day or two, it is less useful in evaluating chronic exposure. Measurement of cotinine can also be useful for identifying

active smokers, as levels generally differ between smokers and nonsmokers exposed to ETS by one to two orders of magnitude.

Characterization of ETS exposure in studies of developmental effects which manifest perinatally or in the first year of life can be particularly challenging. Because of the pronounced effects of maternal smoking during pregnancy on some of the outcomes of interest, studies that can distinguish pre- and postnatal ETS exposure from *in utero* exposure due to maternal active smoking are given more weight. Some studies have attempted to control for maternal active smoking during pregnancy through statistical analyses. However, as spousal smoking habits are correlated, it is difficult to control for the effect of only one partner's smoking. In addition, almost all women who smoke throughout pregnancy continue to smoke after their babies are born (Fingerhut *et al.*, 1990) and thus expose their children both to mainstream tobacco smoke components prenatally and to ETS after birth.

Assessment of current ETS exposure of children is somewhat less problematic. Although concerns similar to those discussed above regarding misclassification remain, children, especially infants and young children, are likely to be exposed to tobacco smoke in fewer circumstances than adults. Cotinine concentrations in children are well correlated with smoking by the mother (Greenberg *et al.*, 1989; U.S. DHHS, 1986); thus, information on cigarette consumption by the mother is likely to provide a reasonable proxy for a young child's ETS exposure. This may not be the case if the mother is not the primary caregiver. The use of paternal smoking alone as a proxy for ETS exposure of infants and children can be problematic, as fathers are generally less likely to be the primary caregiver.

1.3.2 ETS Exposure in Animal Studies

Two main exposure issues arise in examining animal studies of tobacco smoke effects. First, there are no direct analogues of active smoking in animals; in all cases the smoke is dispersed in the air rather than pulled from a cigarette into the lungs. Secondly, in many study reports not enough methodological detail is provided to determine whether the smoke generated can be classified as "mainstream" or "sidestream" smoke, and thus its relevance to ETS exposure is unclear. The majority of the studies available have attempted to simulate active smoking by using mainstream smoke, and some delivered the smoke in bursts or "puffs". A few recent studies have used exposures characterized as "sidestream smoke," which is considered more relevant to the assessment of the effects of ETS exposure.

Animal models have not been prominent in providing evidence concerning the toxicity of active smoking. In contrast to humans, rodents, the most commonly used animals in laboratory experiments, are obligatory nose breathers and cannot inhale through the mouth. In addition, lung and nasal cavity morphometry (e.g., shape) differ significantly between laboratory rodents and humans, leading to differences in distribution and absorption of particulates (Harkema, 1991; Snipes *et al*., 1989). Also, methods of exposing animals to tobacco smoke comparable to human active smoking have not been available. To address this issue, "smoking machines" were developed which provided

"puffs" of smoke drawn through lit cigarettes (Guerin *et al*., 1979). This smoke could be dispersed in a chamber or delivered via "nose only" exposure in which the animal's head was confined in a separate area to which the smoke was delivered. "Nose only" exposures are considered superior to chamber exposures. In chambers, smoke constituents could condense on fur and subsequently be ingested during grooming, although this has not been demonstrated.

Animal models for ETS exposure have been recently developed and studies using such models are being released (Witschi *et al.,* 1997a and b). Typically, "sidestream" smoke is produced from the lit end of a cigarette through which air is drawn to separate "mainstream" smoke. Aging and dilution are provided prior to exposure to simulate constituent profiles similar to those described for human ETS exposure (Coggins *et al*., 1992). Few studies using exposures specifically designed to simulate human ETS exposure have as yet been published, however.

1.3.3 Measures of Effect

The association of ETS exposure and a specific outcome in an epidemiologic study is usually reported as an odds ratio or a rate ratio with a confidence interval, if available from reported studies. Odds and rate ratios adjusted for potential confounders in the original studies are included when available. If not presented in the published report and sufficient data were provided for doing so, crude rate ratios or odds ratios and confidence intervals were calculated. An important consideration in examining causality is whether a dose-response effect was found, so when available those findings are included.

In general, in evaluating the findings of a study, the statistical significance of single comparisons, as indicated by the p-value, is considered. However, when evaluating a body of epidemiologic literature, basing interpretation only on the tallying of statistically significant findings can be misleading (Greenland, 1987; Frieman *et al*., 1978). One problem is that epidemiologic data seldom satisfy the criteria of randomized experimental trials, for which the statistical testing methods were designed. Furthermore, statistical significance is influenced by sample size; not all studies may be large enough to detect a significant association of a given magnitude. This is especially the case if the effect is expected to be of relatively small magnitude, as is anticipated for several of the potential ETS endpoints. Finally, comparisons simply on the basis of p-values do not take into account possible sources of bias in the studies. Therefore, in evaluating causality for a particular endpoint, the overall body of evidence is carefully considered.

1.3.4 Attributable Risk

To provide a context for judging the importance of effects caused by ETS exposure, estimates of ETS-related morbidity and mortality are provided. The estimates are derived from data on prevalence and relative risk, through assessing the attributable fraction, also called the attributable risk (Breslow and Day, 1980; Kelsey *et al.,* 1996). The attributable fraction is the proportion of disease occurrence potentially eliminated if exposure was prevented. U.S. EPA (1992) used an attributable fraction approach in estimating national

figures for ETS-related respiratory health effects. In fact, the national figures derived by U.S. EPA (1992) are used as the basis for deriving California-specific values for childhood asthma induction and exacerbation, bronchitis or pneumonia in young children, and lung cancer: the U.S. estimate is multiplied by 12%, the fraction of the U.S. population residing in the State. U.S. statistics reported in the published literature for ETS-related heart disease mortality (Wells, 1988 and 1994; Steenland, 1992; Glantz and Parmley, 1991) are similarly used to estimate California-specific impacts. In this report, we calculate California-specific values for SIDS, low birth weight, and otitis media, using California prevalence data and relative risk values to first estimate the attributable fraction.

To the extent that smoking prevalence and ETS exposure have been declining in recent years and that California differs from the rest of the country, the California-specific values derived from U.S. estimates may be slightly elevated, depending on the relative impacts of current versus past ETS exposures on the health endpoint. Cases of lung cancer occurring today are a consequence of ETS exposures over past decades, and since smoking prevalence in California was near national levels until the mid-1980s, the differences noted should not significantly impact the accuracy of the California estimate. For heart disease mortality, this issue is more difficult to judge since the importance of current versus past exposures is not clearly understood. Other sources of uncertainty in estimates based on the attributable fraction method include limited information on prevalence of current and past smokers and relative risks of disease associated with smoking status. Methods to describe the sensitivity of these factors to morbidity and mortality estimates derived using an attributable risk formulation have recently been discussed (Taylor and Tweedie, 1997).

1.4 Weight-of-Evidence Evaluations

A “weight-of-evidence” approach has been used to describe the body of evidence on whether or not ETS exposure causes a particular effect. Under this approach, the number and quality of epidemiological studies, as well as other sources of data on biological plausibility, are considered in making a scientific judgment. Associations that are replicated in several studies of the same design or using different epidemiological approaches or considering different sources of exposure are more likely to represent a causal relationship than isolated observations from single studies (IARC, 1996). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess ETS exposure, range in levels of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. General considerations made in evaluating individual studies include study design, appropriateness of the study population, methods used to ascertain ETS exposure, as well as analytic methods, such as the ability to account for other variables that may potentially confound the ETS effect (see for example: IARC, 1996). Increased risk with increasing levels of exposure to ETS is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship (IARC, 1996).

An effect is judged to be causally associated with ETS exposure when a positive relationship between ETS exposure and the effect has been observed in studies in which chance, bias and confounding could be ruled out with reasonable confidence. Effects considered to have suggestive evidence of a causal association with ETS exposure are those for which a causal interpretation can be considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. For several effects it is not possible to judge whether or not ETS exposure affects the severity or prevalence of their occurrence. Either too few studies are available to evaluate the impact, or the available studies are of insufficient quality, consistency or statistical power to permit a conclusion.

Unlike most of environmental contaminants, ETS-related health impacts are directly observable through studies of people in exposure situations that are also experienced by the general population. Still the relative risks observed can be small, requiring a number of studies or large studies to confirm the effect. Some endpoints have not been sufficiently studied epidemiologically, in which case the finding of inadequate evidence should be seen as preliminary. Because the epidemiologic data are extensive, they serve as the primary basis on which findings of ETS effects are made. Experimental data are reviewed to determine the extent to which they support or conflict with the human data. With regard to addressing biological plausibility, analyses based on particular biomarkers should be considered with caution. Presumption of a linear dose-response relationship between ETS exposure as indicated by biomarker measurements and effect can be problematic. The ratio of constituents in mainstream smoke and ETS differs, and constituents differ in their pharmacokinetics properties, as well as in their dose-effect relationships.

TABLE 1.1
ESTIMATED ANNUAL MORBIDITY AND MORTALITY IN NONSMOKERS ASSOCIATED WITH ETS EXPOSURE

Condition	Source	Number of Cases Annually[a]	
		United States	California
Developmental Effects			
Low birthweight	Windham *et al*., 1995	≈ 9,700 - 18,600[b]	≈ 1,200 - 2,200[b]
Sudden Infant Death Syndrome (SIDS)	Klonoff-Cohen *et al.*, 1995	≈ 1,900 - 2,700 deaths[b]	≈ 120 deaths[b]
Respiratory Effects in Children			
Otitis media	Etzel, 1992	0.7 to 1.6 million physician office visits[b]	78,600 - 188,700 physician office visits[b]
New asthma cases	U.S. EPA, 1992	8,000 to 26,000[c]	960-3120[c]
Asthma exacerbation	U.S. EPA, 1992	400,000 to 1,000,000[c]	48,000 to 120,000[c]
Acute lower respiratory illness (LRI) in children up to 18 months	U.S. EPA, 1992	150,000 to 300,000 cases of bronchitis and pneumonia[c] 7,500 to 15,000 hospitalizations[c]	18,000 to 36,000 cases of bronchitis and pneumonia[c] 900 to 1800 hospitalizations[c]
	DiFranza and Lew, 1996	136 - 212 deaths[c]	16 - 25 deaths[c]
Lung Cancer	U.S. EPA, 1992	3000 deaths[c]	360 deaths[c]
	NRC, 1986	2590 to 4040 deaths in 1985	310-485 deaths
Cardiovascular Effects			
Ischemic heart disease	Wells, 1994; Glantz and Parmley, 1991; Steenland, 1992; Wells, 1988	35,000 - 62,000 deaths[c]	4,200 - 7,440 deaths[c]

[a] The numbers in the table are based on maximum likelihood estimates of the relative risk. As discussed in the body of the report, there are uncertainties in these estimates, so actual impacts could be somewhat higher or lower than indicated in the table. The endpoints listed are those for which there is a causal association with ETS exposure based on observations of effects in exposed human populations.

[b] California estimates for low birthweight, SIDS, and middle ear infection (otitis media) are provided in Chapters 3, 4, and 6, respectively. U.S. estimates are obtained by dividing by 12%, the fraction of the U.S. population residing in California.

[c] Estimates of mortality in the U.S. for lung cancer and respiratory effects, with the exception of middle ear infection (otitis media), come from U.S. EPA (1992). U.S. range for heart disease mortality reflects estimates reported in Wells (1988 and 1994), Glantz and Parmley (1991), Steenland (1992). California predictions are made by multiplying the U.S. estimate by 12%, the fraction of the U.S. population residing in the State. Because of decreases in smoking prevalence in California in recent years, the number of cases for some endpoints may be somewhat overestimated, depending on the relative impacts of current versus past ETS exposures on the health endpoint.

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